REMARKS / ARGUMENTS

Claims 69-75, 77, 78, 81-106 are currently pending in the application. Claim 69 has been amended. No new matter has been added by way of this amendment, and support can be found in the specification, *e.g.*, at page 21, lines 11-35). Applicants respectfully request reconsideration of pending claims 69-72, 75, 77, 78, and 81-106.

I. Rejection Under 35 U.S.C. § 112, First Paragraph (Written Description)

The Examiner has made a number of rejections under 35 U.S.C. § 112, first paragraph regarding alleged lack of written description. For clarity, each of these rejections will be discussed separately.

A. Claims 69-72, 75, 77, and 88-91

The Examiner has rejected claims 69-72, 75, 77, and 88-91 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention at the time the application was filed (Office Action, parts 6-7).

Applicants respectfully traverse this ground of rejection.

The Examiner opines that the claims recite added material not supported by the original disclosure. Specifically, the Examiner alleges that the specification does not provide support for the recitation of "comprising greater than 80% identity with the amino acid sequence depicted in SEQ ID NO:2," and the "definition of 'about' does not identify a sequence that is 80% identical to SEQ ID NO:2" (Office Action, part 7; emphasis added).

Applicants respectfully direct the Examiner's attention to the passage on page 21, lines 33-35 of the specification , which states that:

> two amino acid sequences are "substantially homologous" or "substantially similar" when greater than 70% of the amino acid sequences are identical, or greater than about 90% are similar (functionally similar).

(emphasis added). The specification also states that "sequence similarity" refers to "the degree of identity...between...amino acid sequences" (specification, page 21, lines 17-18; emphasis added). The specification further defines the term "about" to mean "within 20%, preferably within 10% and more preferably within 5% of a given range" (page 16, lines 6-7; emphasis added). Thus, "about 90%" means, *inter alia,* 90% ± 10% (*i.e.*, 80%). Thus, contrary to the Examiner's assertions, "80% identity" is expressly disclosed in the specification.

However, solely in an effort to advance prosecution of this application, claim 69 has been amended to recite that "the Smurf has an amino acid sequence similarity of greater than 80% with the amino acid sequence depicted in SEQ ID NO:2." Applicants submit that the scope of the claim has not been changed by way of this amendment, and no new matter has been added, as evidenced by, *e.g.,* the passages referred to above (*e.g.,* page 21, lines 11-35 and page 16, lines 6-7).

Accordingly, reconsideration and withdrawal of this ground of rejection is respectfully requested.

B. Claims 69-72, 75, 77, and 81-91

The Examiner has rejected claims 69-72, 75, 77, and 81-91 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention at the time the application was filed (Office Action, parts 8-9).

Applicants respectfully traverse this ground of rejection.

The Examiner opines that the recitation in claim 69 of "WW domain and/or a HECT domain" provides "some additional structural information, however does not provide any functional limitation, as possession of a domain is not *per se* a function" (Office Acton, part 8). However, the specification states that the HECT domain has the catalytic activity needed for ubiquitination of Smads, and the WW domain interacts with the PPXY domains of Smads (*see, e.g.*, page 14, lines 25-27). Thus, contrary to the Examiners assertion, possession of a

WW or HECT domain indeed correlates with domain functional activity (*e.g.*, Smad PPXY domain interaction and/or Smad ubiquitination).

The Examiner also opines that the recitations of 80% or 90% sequence identities "does not provide adequate description of the genus of polypeptides encompassed in the claims. There is no indicia as to conserved regions of for example SEQ ID NOS: 2 and 4 or where in the sequences the modifications will occur" (Office Action, part 6).

At the outset, Applicants point out that there is no sequence identity requirement for claims 78, and 81-87. In fact, independent claim 78 (not rejected) and claims 81-87 (rejected, but depend on claim 78) each recite that the Smurf activity detected is "activity of a Smurf comprising the amino acid sequence depicted in SEQ ID NO:4." Similarly, claim 75 recites that the "activity of a Smurf comprising the amino acid depicted in SEQ ID NO:2." Thus, Applicants submit that the "genus of polypeptides encompassed by [at least these] claims" is adequately described.

With respect to independent claim 69, and claims 70-72, 75, 77, and 88-91 (which depend on claim 69), Applicants submit that these claims also comply with the written description requirement.

As the Examiner is aware, the written description requirement of 35 U.S.C. § 112, first paragraph, does not require a description of the complete structure of every species within a chemical genus. See, *e.g., Utter v. Hiraga*, 845 F.2d 993, 998 (Fed. Cir. 1988) ("A specification may, within the meaning of 35 U.S.C. § 112, ¶ 1, contain a written description of a broadly claimed invention without describing all species that claim encompasses.") A "description of a genus of cDNAs may be achieved by means of... a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." *University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997). Additionally, "the written description requirement can be met by 'show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics...*i.e.*, complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of characteristics." *Enzo Biochem, Inc. v. Gen-*

Probe Inc., 296 F.3d 1316, 1324 (Fed. Cir. 2002) (emphasis added). While the claims recite polypeptides, and not DNA as in *Lilly* and *Enzo*, the same standard applies. *See University of Rochester v. G.D. Searle & Co., Inc.*, 358 F.3d 916 (Fed. Cir. 2004) ("We agree with Rochester that *Fiers*, *Lilly,* and *Enzo* differ from this case in that they all related to genetic material whereas this case does not, but we find that distinction to be unhelpful to Rochester's position. It is irrelevant, the statue applies to all types of inventions. We see no reason for the rule to be any different when non-genetic materials are at issue.")

Here, the complete structure of SEQ ID NO:2 is explicitly described, and the polypeptides in the genus recited in claims 69-72 and 77 share at least 80% identity with the structure of SEQ ID NO:2. Thus, the structural features that are common to the genus make up at least 80% of the structure set forth in SEQ ID NO:2. Respectfully, the Examiner has not adequately explained why this degree of structural similarity is inadequate to constitute a "substantial portion of the genus," as required in *Lilly*. In addition to the identity to SEQ ID NO:2, dependent claims 70-72 and 88-89 also recite a particular Smurf activity (or function) that is being detected in the claimed methods, which further supplement the requirements of *Lilly*.

Moreover, the claims currently recite that the Smurf comprise a WW domain and/or HECT domain That is, the claims recite a genus that share at least 80% identity with the structure of SEQ ID NO:2 and contain a WW and/or HECT domain. Thus, independent claim 69 recites "a conserved region" and "what composition of amino acids is present or absent in SEQ ID NO:2." The Examiner has offered no evidence as to why he believes that a Smurf comprising (1) a WW domain and/or a HECT domain, and (2) comprising an amino acid sequence similarity of greater than 80% with the amino acid sequence depicted in SEQ ID NO:2 would have an activity (*e.g.,* Smad ubiquitination, or interaction with a Smad PPXY domain) that is any different than, *e.g.,* the Smurf having the amino acid sequence depicted in SEQ ID NO:2.

The Examiner is also directed to the Revised Interim Written Description Guidelines Training Materials (discussed by the Examiner in the Office Action on page 8, part 9), which state that a claim to a protein having a given SEQ ID NO. and variants thereof having a sequence similarity of 95% and that catalyze a reaction A→ B comply with the written

description requirement. In this Training Materials example, the specification discloses the sequence, and the procedures for making variants of the sequence are "conventional in the art." Moreover, the single species disclosed in the Training Materials example is representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of an assay which applicant provided for identifying all of the at least 95% identical variants of the sequence which are capable of the specified catalytic activity. Accordingly this Training Materials example claim was deemed to satisfy the written description requirement.

Here, Applicants have similarly provided the reference sequence. Additionally, the specification provides extensive guidance at pages 24-27 as to how to obtain other Smurf derivatives (*e.g.*, insertions, deletions, substitutions, *etc.*), using techniques "conventional in the art." at the time the application was filed (*see*, *e.g.*, Sambrook *et al.*, 1989, cited on page 26, line 29 of the specification).

Moreover, in all cases the Smurf used in the assays has a conserved WW and/or HECT domain. As discussed above, these conserved domains allow, *e.g.*, Smad protein ubiquitination or Smad PPXY domain interaction. Indeed, dependent claims 70-72 and 88-89 recite a specific Smurf activity (or function) that is being detected in the claimed methods. Assays for these activities (or functions), *e.g.*, Smad ubiquitination, are disclosed in the specification (*see, e.g.*, page 60, lines 3-17) and well-known in the art.

Thus, for at least the reasons discussed above, Applicants submit that claims 69-72, 75, 77, and 81-91 comply with all the requirements of 35 U.S.C. § 112, first paragraph. Accordingly, reconsideration and withdrawal of this ground of rejection is respectfully requested.

C. Claims 92-106

The Examiner has rejected claims 92-106 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention at the time the application was filed (Office Action, parts 10-11).

Applicants respectfully traverse this ground of rejection.

At the outset, Applicants submit that--contrary to the examiner's assertions--claims 97-99 added in the Response dated March 7, 2005 were indeed identical to claims 70-72 (rewritten in independent form) as these claims existed October 6, 2004 when the Examiner indicated they were allowable. As of the October 6, 2004 Office Action, pending claims 69-72 were as follows:

> 69. A method of screening for a modulator of Smurf activity which comprises detecting modulation of Smurf activity in the presence of a test compound relative to Smurf activity in the absence of the test compound.
>
> 70. The method according to claim 69, wherein the Smurf activity is ubiquitination of a Smad polypeptide in a host cell.
>
> 71. The method according to claim 69, wherein the Smurf activity is interaction of a Smurf WW domain with a PPYX [*sic* PPXY] domain of a Smad polypeptide.
>
> 72. The method according to claim 71, wherein the test compound is screened for the ability to inhibit the interaction.

In the October 6, 2004 Office Action, the Examiner indicated these claims 70-72 would be allowable if rewritten in independent form (page 11). As such, new claims 97-99 were added in the Response dated March 7, 2005:

> 97. A method of screening for a modulator of Smurf activity which comprises detecting modulation of Smurf activity in the presence of a test compound relative to Smurf activity in the absence of the test compound, wherein the Smurf activity is ubiquitination of a Smad polypeptide in a host cell.
>
> 98. A method of screening for a modulator of Smurf activity which comprises detecting modulation of Smurf activity in the presence of a test compound relative to Smurf activity in the absence of the test compound, wherein the Smurf activity is interaction of a Smurf WW domain with a PPXY domain of a Smad polypeptide.
>
> 99. The method according to claim 94 [*sic* 98], wherein the test compound is screened for the ability to inhibit the interaction.

Thus, Applicants respectfully disagree with the examiner's assertion that claims 97-99 required "a structure, which claims 70-72 had" and that claims 70-72 "were not written with all the pertinent information from independent claim 69." (Office Action, part 11). Indeed, claims 97-99 were identical to claims 70-72 rewritten in independent form, and contained all of the limitations of claim 69, as of October 6, 2004 when the claims were held allowable.

Next, the Examiner opines that, "[c]laim 92, for example does not set forth which Smurf's activity is being monitored, as the art recognizes Smurf1, Smurf2, and Dsmurf as being distinct" (Office Action, part 11). Respectfully, Applicants submit that which type of Smurf activity being monitored, *e.g.,* in claim 92 is not important. Indeed, claim 92 recites a method of screening for a modulator of ubiquitination of a Smad polypeptide (a "Smurf activity") in the presence of a test compound relative to ubiquitination of a Smad polypeptide in the absence of the test compound. Similarly, claim 93 recites a method of screening for a modulator of ubiquitination of a TGFβ receptor (a "Smurf activity") in the presence of a test compound relative to ubiquitination of a TGFβ receptor in the absence of the test compound. In fact, each of these claims specifically sets forth the particular Smurf activity being screened for, *e.g.,* ubiquitination of a Smad polypeptide (claims 92, 94, and 97, 104), ubiquitination of a TGFβ receptor (claim 93, 95, 96 and 105), and interaction of a Smurf WW domain with a PPXY domain of a Smad polypeptide (claim 98, 99-101, and 106). As a result, Smurf 'structure" is irrelevant.

Thus, for at least these reasons, Applicants submit that claims 92-106 comply with all the requirements of 35 U.S.C. § 112, first paragraph. Accordingly, reconsideration and withdrawal of this ground of rejection is respectfully requested.

D. Claims 78-87

The Examiner has rejected claims 78-87 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention at the time the application was filed (Office Action, part 12)

Applicants respectfully traverse this ground of rejection.

To begin with, Applicants note that claims 79-80 have been previously cancelled. Thus, the rejection is only applicable to claims 78 and 81-87.

The Examiner opines that "the claims do not specify what Smurf activity is being monitored" (Office Action, part 12. However, Applicants respectfully point out that each of claims 81-85 do, in fact, specifically recite a Smurf activity.

The Examiner also opines that the "instant specification on page 24 outlines wild type Smurf1 or Smurf2 (vertebrates) and the art recognizes Dsmurf, (Drosophila) which are said to have different functions, thus without a reference point a skilled artisan would not be able to practice the claimed invention.(Office Action, part 12). However, claim 78 and 81-87 each recite that the Smurf activity detected is "activity of a Smurf comprising the amino acid sequence depicted in SEQ ID NO:4." That is, SEQ ID NO:4 (human Smurf2) is the "reference point."

Thus, for at least these reasons, Applicants submit that claims 78 and 81-87 comply with all the requirements of 35 U.S.C. § 112, first paragraph. Accordingly, reconsideration and withdrawal of this ground of rejection is respectfully requested.

II. Rejection Under 35 U.S.C. § 112, First Paragraph (Enablement)

Claims 69-72, 75, 77 and 88-91 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement (Office Action, parts 13-14).

Applicants respectfully traverse this ground of rejection.

MPEP § 2164.01 states that 35 U.S.C. § 112, first paragraph, "has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation." The same section further states that "[t]he fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation."

Applicants submit that one of ordinary skill in the art would know how to identify and utilize Smurf polypeptides for use in the methods of the invention without undue experimentation. For example, the specification provides extensive guidance as to how to

clone Smurf family genes (*e.g.*, at pages 23-24) and express Smurf family proteins (*e.g.*, at pages 27-39). The Examiner is also directed to Example 1, wherein human, mouse and *Xenopus* Smurf1 were identified, and to Example 2, wherein human and mouse Smurf2 were identified using techniques disclosed in the specification and well-known in the art. Additionally, the specification provides extensive guidance at pages 24-27 as to how to obtain Smurf derivatives (*e.g.*, insertions, deletions, substitutions, *etc.*), using techniques well-known to skilled artisans at the time the application was filed (*see, e.g.*, Sambrook *et al.*, 1989, cited on page 26, line 29 of the specification) Further, the specification provides additional guidance at pages 41-46 as to how to use the Smurf family proteins in various routine *in vitro* and *in vivo* screening assays.

The Examiner also opines that the "amount of experimentation necessary to practice the claimed invention is undue as the claims encompass an unspecified amount of peptide fragments. The instant specification indicates that 'Smurf proteins of the invention may contain at least about 5 and preferably at least 10 contiguous amino acids from the sequences set forth in SEQ ID NOS:2/4' (see page 4)...However, the specification does not demonstrate any fragments of the claimed sequence having Smurf activity." (Office Action, part 13). The Examiner also opines that "the skilled artisan cannot envision the detailed chemical structure of the claimed Smurf protein having 20% variability absent guidance as to where in the sequence the changes are made and what changes are made" (Office Action, Part 14).

However, Applicants respectfully submit that Applicants have enabled SEQ ID NOS: 2 and 4 and fragments thereof by providing the complete amino acid sequence of SEQ ID NOS: 2 and 4, and thus one skilled in the art could envision Smurf having greater than 80% sequence similarity with SEQ ID NO:2. Additionally, Applicants have provided extensive guidance as to how to create mutants and derivatives of Smurf. (*see, e.g.*, page 24, line 15 - page 27, line 10). Respectfully, the Examiner has provided no reasoning for her conclusion that other fragments of SEQ ID NOS: 2 or 4 could not be similarly used in the methods of the claimed invention. Even if some of the species in a genus claim are inoperative, the claims are not necessarily invalid. *Atlas Powder Co. v. E.I. Du Pont de Nemours & Co.*, 750 F.2d 1569, 1576; 224 U.S.P.Q. (BNA) 409. "It is not a function of the claims to specifically exclude...possible inoperative substances...." *Id. (citing In re Dinh-Nguyen,* 492 F.2d 856,

858-59, 181 U.S.P.Q. (BNA) 46, 48 (CCPA 1974) (emphasis omitted); *accord, In re Geerdes,* 491 F.2d 1260, 1265, 180 U.S.P.Q. (BNA) 789, 793 (CCPA 1974); *In re Anderson,* 471 F.2d 1237, 1242, 176 U.S.P.Q. (BNA) 331, 334-35 (CCPA 1973)).

The Examiner further opines that a "making and testing the infinite number of possible variants to find one that functions as described is undue experimentation" (Office Action, part13). However, it was routine at the time the application was filed to screen large amounts of mutants, for example in high-throughput screening assays, for functional activity. See, *e.g.,* MPEP § 2164.01 ("[t]he fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation.").

Thus, Applicants submit that claims 69-72, 75, 77 and 88-91 are fully enabled and comply with all the requirements of 35 U.S.C. § 112, first paragraph. Accordingly, reconsideration and withdrawal of this ground of rejection is respectfully requested.

III. Conclusion

In view of the foregoing remarks, Applicants respectfully submit that this application is now in condition for allowance. If a telephone interview would advance prosecution of the application, the Examiner is invited to call the undersigned at the number listed below.

A Petition for a one (1) month Extension of Time under 37 C.F.R. § 1.136(a) is filed concurrently herewith (in duplicate), which extends the response period from December 27, 2005 to and including January 27, 2006. The Petition further authorizes the PTO to charge the one month extension fee of $120 to our Deposit Account No. 50-3013. No additional fees are believed due in connection with this Amendment. However, if there are any other fees due, please charge them to Deposit Account 50-3013. If a request for extension of time and fee are required under 37 C.F.R. § 1.136 that have not been accounted for, such an extension

is requested and the fee should be charged to our Deposit Account. Also, please charge any fees underpaid or credit any fees overpaid to the same Deposit Account.

Respectfully submitted,

Date: Jan. 27, 2006

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